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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/575,736	10/11/2006	Michael V. Agrez	65350US(54086)	9415

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EXAMINER	
DUFFY, BRADLEY	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/575,736	AGREZ, MICHAEL V.	
	Examiner	Art Unit	
	BRADLEY DUFFY	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *20 April 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 86-107* is/are pending in the application.

4a) Of the above claim(s) *97* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,86,96 and 98-107* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 April 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/13/06,3/14/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The species election with traverse filed April 20, 2010, is acknowledged and has been entered.

Applicant has elected the species of signal peptide of a signal peptide comprising the amino acid sequence of SEQ ID NO:1, the species of β integrin subunit of β6 and the species of cancer of colon cancer for the elected invention of the Group XII, drawn to a method for treatment of a cancer in a mammal, wherein cancer cells of the cancer express a MAP kinase and the method comprises treating the mammal with an effective amount of a polypeptide that consists of SEQ ID NO:7. Additionally, as detailed below, after further consideration the invention of Group IX, drawn to a method for treatment of a cancer in a mammal, wherein cancer cells of the cancer express a MAP kinase and the method comprises treating the mammal with an effective amount of a polypeptide that consists of SEQ ID NO: 4 has been rejoined with the elected invention. No other Groups have been rejoined. Claims 1, 86-96 and 98-107 read on the elected species.

2. Claims 1 and 86-107 are pending in the application. Claim 97 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species of invention, there being no allowable generic or linking claim.

3. Claims 1, 86-96 and 98-107 are under examination.

Election/Restrictions

4. Applicant's traversal of the restriction and election requirement set forth in the previous office actions is acknowledged.

Applicant's arguments have been carefully considered but have not been found persuasive for the following reasons:

In the response filed May 1, 2009, Applicant traverses the restriction requirement and appears to be arguing that the claimed invention is distinguished over Agrez

because it is based on the surprising discovery that it is not necessary for the integrin to which the MAP kinase binds to be expressed by a target cancer cell in order to inhibit growth of the cancer cells, while Agrez relates to the inhibition of the integrin MAP kinase interaction and in contrast it is the non-expression of the β integrin that is the subject of the present application.

In response, these arguments are not found persuasive because it is aptly noted that the claimed process does not recite that the β integrin is not expressed by the cancer. Notably, claim 1 recites that the β integrin is ***essentially*** not expressed, which reasonably encompasses cancers where the β integrin is expressed. Accordingly, the Examiner respectfully disagrees that the claimed invention distinguishes from Applicant's characterization of Agrez.

Secondly, Applicant argues that there would be no search burden to examine the Groups together.

In response, unity of invention restriction practice for national stage applications does not require that there be a serious search burden when making a lack of unity of invention requirement (see MPEP 1893.03(d)).

Secondly, in the response filed April 20, 2010, Applicant has traversed the species requirements and appears to be arguing that that the various species represent different embodiments of a single inventive concept which is treatment of cancer cells with a polypeptide that binds to a binding domain of a MAP kinase for a β integrin subunit wherein the β integrin subunit is essentially not expressed by the cancer cells and that other alternative species could be employed in this single inventive concept.

In response, this argument is not found persuasive because, as set forth above, treatment of cancer cells with a polypeptide that binds to a binding domain of a MAP kinase for a β integrin subunit wherein the β integrin subunit is essentially not expressed by the cancer cells is not a single inventive concept as such a method is not distinguished over the prior art.

Applicant is reminded upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise

require all the limitations of an allowable generic claim as provided by 37 CFR 1.141. However, as detailed below, there is presently no allowable generic claim.

Finally, after further consideration, Group IX, drawn to a method for treatment of a cancer in a mammal, wherein cancer cells of the cancer express a MAP kinase and the method comprises treating the mammal with an effective amount of a polypeptide that consists of SEQ ID NO: 4 has been rejoined with the elected invention. This invention has been rejoined because a peptide consisting of the amino acid sequence of RSKAKNPLYR, i.e., the amino acid sequence of SEQ ID NO:7 differs from the amino acid sequence of SEQ ID NO:4 by the deletion of the underlined amino acids of RSKAKWQTGTNPLYR of SEQ ID NO:4.

Therefore, for these reasons and the reasons set forth in the previous office action, the inventions do not share unity of invention as required under PCT Rule 13 and the different species do not share the same or corresponding special technical feature so as to form a single general inventive concept under PCT Rules 13.1 and 13.2. Accordingly, while Group IX has been rejoined for the reason set forth above, the restriction/election requirement is otherwise deemed proper and therefore made FINAL.

Information Disclosure Statement

5. The references cited in the information disclosure statements filed April. 13, 2006, and March 14, 2007, have been considered.

Claim Objections

6. Claims 1, 86-96 and 98-107 are objected to because of the following informalities: These claims are drawn in the alternative to the subject matter of non-elected inventions and/or non-elected species of invention.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1, 86-96 and 98-107 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 86-96 and 98-107 are indefinite for reciting that "the β integrin subunit is ***essentially*** not expressed by the cancer cells" in claim 1. This renders the claims indefinite because it is unclear what level of expression of the β integrin subunit by the cancer cells is allowed and the cancer cells still be considered to ***essentially*** not express the β integrin subunit. In this case, the specification does not provide any explicitly limiting standard for separating cancer cells that ***essentially*** do not express the β integrin subunit from those that do ***essentially*** express the β integrin subunit. For example, depending on the level of the β integrin subunit that can expressed by the cancer before the cells are no longer considered to ***essentially*** not express the β integrin, the cancers cells encompassed by the method will vary widely, such that different cancers cells would be encompassed depending on the level used. Therefore, the metes and bounds of the subject matter that Applicant regards as the invention will also vary widely, so that the metes and bounds cannot be unambiguously determined; accordingly, these claims fail to delineate the metes and bounds of the subject matter that Applicant regards as the invention with the requisite particularity and clarity to satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

Accordingly, these claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of

> making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1, 86-96 and 98-107 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

The considerations that are made in determining whether a claimed invention is supported by an adequate written description are outlined by the published Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, para. 1, ``Written Description'' Requirement (Federal Register; Vol. 66, No. 4, January 5, 2001; hereinafter "Guidelines"). A copy of this publication can be viewed or acquired on the Internet at the following address: <http://www.gpoaccess.gov/>.

These guidelines state that rejection of a claim for lack of written description, where the claim recites the language of an original claim should be rare. Nevertheless, these guidelines further state, "the issue of a lack of written description may arise even for an original claim when an aspect of the claimed invention has not been described with sufficient particularity such that one skilled in the art would recognize that the applicant has possession of the claimed invention" (*Id.* at 1105). The "Guidelines" continue:

> The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art. This problem may arise where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A lack of adequate written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process.

With further regard to the proposition that, as *original* claims, the claims themselves provide *in haec verba* support sufficient to satisfy the written description requirement, the Federal Circuit has explained that *in ipsis verbis* support for the claims

in the specification does not *per se* establish compliance with the written description requirement:

> Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Regents of the University of California v. Eli Lilly & Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). *See also:* University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 1892 (CA FC 2004).

Thus, an original claim may provide written description for itself, but it must still be an adequate written description, *which establishes that the inventor was in possession of the invention*.

In the instant case, claims 1, 86-96 and 98-107 are broadly drawn to methods for the treatment of a diverse genus of cancers in a mammal, wherein cancer cells of the cancer express a structurally and functionally diverse genus of MAP kinases by treating the mammal with an effective amount of a structurally and functionally diverse genus of polypeptides that bind to a binding domain of the MAP kinase for a cytoplasmic binding domain of β integrin subunit for the MAP kinase, and the β integrin subunit is essentially not expressed by the cancer cells. Dependent claims further recite that the polypeptide comprises a modified amino acid sequence compared to the binding domain of the β integrin subunit and the modified amino acid sequence has sufficient amino acid sequence homology with the binding domain of the β integrin subunit to bind to the binding domain of the MAP kinase, that the modified amino acid sequence comprises the binding domain of the β integrin subunit in which one or more amino acids in a linker region of the binding domain non-essential for the binding of the MAP kinase have been deleted, that the linker region of the binding domain has been deleted in the modified amino acid sequence, that the linker region binds opposite end regions of the binding domain of the β integrin subunit together and the end regions are unchanged in the modified amino acid sequence compared to the binding domain of the β integrin

subunit, that the modified amino acid sequence has at least 50% overall amino acid sequence homology with the binding domain of the β integrin subunit, that the polypeptide has a length of greater than 5 and up to 15 amino acids or that the polypeptide comprises the binding domain of the β integrin subunit for the MAP kinase. Additionally, dependent claims further recite that the polypeptide is coupled to a structurally and functionally diverse genus of facilitator moieties that facilitate passage of the polypeptide across the outer cell membrane of the cancer cells or that the facilitator moiety comprises a partial sequence of a signal peptide, or a modified form thereof.

Notably, as a first point, the claims do not require that the recited genus of "polypeptides that binds to a binding domain of the MAP kinase for a cytoplasmic binding domain of β integrin subunit for the MAP kinase" or the recited genus of "facilitator moieties that facilitate passage of the polypeptide across the outer cell membrane of the cancer cells" have any particular structure and therefore, there can be no correlation of any particular identifying structural feature with any function of the recited polypeptides or facilitator moieties. In this case, it is noted that the specification does not adequately describe the genus of "polypeptides that binds to a binding domain of the MAP kinase for a cytoplasmic binding domain of β integrin subunit for the MAP kinase" or the recited genus of "facilitator moieties that facilitate passage of the polypeptide across the outer cell membrane of the cancer cells" as having any particularly identifying structural feature which would allow one of skill in the art to immediately envision or recognize a "polypeptide that binds to a binding domain of the MAP kinase for a cytoplasmic binding domain of β integrin subunit for the MAP kinase" or a "facilitator moiety that facilitates passage of the polypeptide across the outer cell membrane of the cancer cells" from any other peptide. For example, the specification at page 16 sets forth that the polypeptides encompassed by the genus are described by their functional activity alone, i.e., binding to a binding domain of the MAP kinase and at page 19 that the moieties are described by their functional activity alone, i.e., facilitating entry of the polypeptide into cells.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or by describing structural features common to that genus that "constitute a substantial portion of the genus." See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997): "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNA, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus."

While, the inventions at issue in Lilly were DNA constructs *per se*, the analysis in this case is also applicable to the "complement inhibitors" at issue here which may be any protein or carbohydrate inhibitor and the court has since clarified that this standard applies to compounds other than cDNAs. See University of Rochester v. G.D. Searle & Co., Inc., F.3d, 2004 WL 260813, at *9 (Fed.Cir.Feb. 13, 2004). Further, a disclosure that does not adequately describe a product logically cannot adequately describe a method of treating cancer using that product.

Notably, with particular regard to the use of use functional language to define the boundaries of a claimed genus the Federal Circuit has recently clarified:

> For example, a generic claim may define the boundaries of a vast genus of chemical compounds, and yet the question may still remain whether the specification, including original claim language, demonstrates that the applicant has invented species sufficient to support a claim to a genus. The problem is especially acute with genus claims that use functional language to define the boundaries of a claimed genus. In such a case, the functional claim may simply claim a desired result, and may do so without describing species that achieve that result. But the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus. Ariad Pharmaceuticals, Inc. v. Eli Lilly and Co. (Fed. Cir. 2010 <http://www.cafc.uscourts.gov/opinions/08-1248.pdf>) (En Banc Decision).

In this case, the instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features that are common to the genera. That is, the specification provides neither a representative number of polypeptides that bind to a binding domain of the MAP kinase for a cytoplasmic binding

domain of β integrin subunit for the MAP kinase or facilitator moieties that facilitate passage of the polypeptide across the outer cell membrane of the cancer cells or that the facilitator moiety comprises a partial sequence of a signal peptide, or a modified form thereof that encompass the genera nor does it provide a description of structural features that are common to the genera. Structural features that could distinguish the claimed genera from others not encompassed by the genera are missing from the disclosure. No common structural attributes identify the members of the genera. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is needed. Since the disclosure fails to describe common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosure of some known species of encompassed by the genera in the specification is insufficient to describe the genera because these species are not representative of the claimed genera or subgenera. In this case, the specification merely presents functional language that recites a desired result without describing sufficient species that achieve that result. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to adequately describe the methods as broadly claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). Even if Applicant proposes methods of screening for possible members of the genus, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation.

By way of further explanation, neither the claims nor the specification require that the recited polypeptides that bind to a binding domain of the MAP kinase for a

cytoplasmic binding domain of β integrin subunit for the MAP kinase or facilitator moieties that facilitate passage of the polypeptide across the outer cell membrane of the cancer cells or that the facilitator moiety comprises a partial sequence of a signal peptide, or a modified form thereof for use in methods of treating cancer have any particular structure and therefore, there can be no correlation of any particular identifying structural feature with any function of the recited compounds. Accordingly, the genera encompass a diverse genus of peptides and one of skill in the art could not immediately envision, recognize or identify the structure of the claimed genera which would be effective in methods of treating cancer.

To further explain why the claimed methods which recite structurally and functionally diverse "polypeptides that bind to a binding domain of the MAP kinase for a cytoplasmic binding domain of β integrin subunit for the MAP kinase" are not adequately described, it is noted that it is well-established in the art that there is a high degree of unpredictability in modeling and predicting agents which will bind to any particular protein and inhibit that protein. For example, according to Tame (J. Comput. Aided Mol. Des. 1999 Mar; 13 (2): 99-108), for example, computational approaches to design or select drug reagents which bind protein targets are hindered by the complexity of the physical chemistry that underlies weak, non-covalent interactions between protein targets (e.g., a cell surface receptor) and small molecule ligands (e.g., peptides); see entire document (e.g., the abstract). In addition, Dixon (Proteins. 1997; Suppl 1: 198-204) points out that the evaluation (scoring) of potential solutions is still an area that needs improvement, especially when predicting protein-protein interaction because of limitations associated with reproducing the geometry of the complex; see entire document (e.g., the abstract). While there are many additional reasons that predictions based upon the results of such modeling approaches are inaccurate, it is noted that Lensink et al. (Proteins. 2007; 69: 704-718) very recently reviewed the performance accuracy of various different methods for predicting protein-protein interaction, reporting that significant numbers of "incorrect" determinations were made in blind analyses (i.e., without knowledge of the "correct" answer); see entire document (e.g., page 706, Table

I). Lensink et al. concludes accordingly that their results "do not reveal a striking breakthrough in docking performance" in the past several years, despite some encouraging progress (page 717, column 1); and given such predictive inaccuracies, Lensink et al. adds that “current scoring methods are probably not sensitive enough” (abstract). Accordingly, one of skill in the art would not recognize that Applicant was in possession of the claimed methods for this reason as well.

Furthermore, while the specification provides species polypeptides that can bind to the MAP kinase ERK2 such as a polypeptide consisting of the amino acid sequence of RSKAKWQTGTNPLYR (SEQ ID No: 4) or RSKAKNPLYR (SEQ ID No: 7), that have the function of inhibiting human cancers expressing ERK2 (see page 34), these species would not be considered to be representative of other peptides that bind to ERK2 or representative of other MAP kinases which can be inhibited to treat cancers because as set forth above, it is well-established in the art that there is a high degree of unpredictability in modeling and predicting agents which will bind to any particular protein and inhibit that protein. In this case, the claims are drawn to diverse peptides that bind any MAP kinase from any species, and while one of skill in the art would recognize that a polypeptide consisting of the amino acid sequence of RSKAKWQTGTNPLYR (SEQ ID No: 4) or RSKAKNPLYR (SEQ ID No: 7) would be effective to inhibit a human cancer expressing ERK2, they would not be able to immediately envision whether these polypeptides would treat other cancers expressing other MAP kinases and they would not be able to immediately envision the structure of other peptides that bind to a MAP kinase and inhibit cancer.

Once again, it is not sufficient to define a substance solely by its principal biological property, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. Per the *Enzo* court’s example, (*Enzo Biochem, Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609 (CA FC 2002) at 1616) of a description of an anti-inflammatory steroid, i.e., a steroid (a generic structural term) couched “in terms of its function of lessening inflammation of tissues” which, the court stated, “fails to distinguish any steroid from others having the same activity or function”. Similarly, the function of “binding to a binding domain of the

MAP kinase" does not distinguish any "polypeptide" from others having the same activity or function and as such, fails to satisfy the written-description requirement. Applicant has not disclosed any relevant, identifying characteristics, such as structure or other physical and/or chemical properties, sufficient to show possession of the claimed genera or subgenera. Mere idea or function is insufficient for written description; isolation and characterization at a minimum are required. A description of what a material does, rather than what it is, usually does not suffice. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406.

Additionally, "generalized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

In this case, the specification merely discloses that other polypeptides as encompassed by the claimed genus or subgenera could be screened for using various techniques (see page 17). Although the skilled artisan could potentially screen for other "polypeptides" as encompassed by the claims to identify those that bind a MAP kinase binding domain" and then further screen those "polypeptides" to identify those that inhibit a particular cancer, it is duly noted that the written description provision of 35 U.S.C § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought,

he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). In this case, the skilled artisan cannot envision the detailed structure(s) of the genera or subgenera of "polypeptides that bind to a binding domain of the MAP kinase for a cytoplasmic binding domain of β integrin subunit for the MAP kinase", "polypeptides comprising a modified amino acid sequence compared to the binding domain of the β integrin subunit and the modified amino acid sequence has sufficient amino acid sequence homology with the binding domain of the β integrin subunit to bind to the binding domain of the MAP kinase", "polypeptides that comprise modified amino acid sequences of the binding domain of the β integrin subunit in which one or more amino acids in a linker region of the binding domain non-essential for the binding of the MAP kinase have been deleted", "polypeptides in which the linker region of the binding domain has been deleted in the modified amino acid sequence", "polypeptides in which the linker region binds opposite end regions of the binding domain of the β integrin subunit together and the end regions are unchanged in the modified amino acid sequence compared to the binding domain of the β integrin subunit", "polypeptides comprising a modified amino acid sequence that has at least 50% overall amino acid sequence homology with the binding domain of the β integrin subunit", "polypeptides having a length of greater than 5 and up to 15 amino acids" or "polypeptides comprising the binding domain of the β integrin subunit for the MAP kinase" that would be effective to treat cancer, and, therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Then to further address the written description of the genera of "facilitator

moieties that facilitate passage of the polypeptide across the outer cell membrane of the cancer cells" or the "facilitator moieties comprising a partial sequence of a signal peptide, or a modified form thereof" as set forth in claims 94 and 95, respectively, it is established in the art that there is a high degree of unpredictability in determining the structure of a given protein because a protein's structure is dependent on its given amino acid sequence and cannot be determined *a priori* and the function of a given protein is also highly unpredictable and variable and cannot necessarily be linked to a given structure. As evidenced by Jones (Pharmacogenomics Journal, 1:126-134, 2001), protein structure "prediction models are still not capable of producing accurate models in the vast majority of cases" (page 133, 3rd paragraph). Furthermore, Tosatto et al state, "the link between structure and function is still an open question and a matter of debate" (Current Pharmaceutical Design, 12:2067-2086, 2006, page 2075, 1st new paragraph). Additionally, Skolnick et al. (*Trends in Biotechnology* 2000; **18**: 34-39), for example, discloses that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (see, e.g., the abstract; and page 34, *Sequence-based approaches to function prediction*). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see, in particular, the abstract and Box 2). Therefore, it is apparent that one of skill in the art would not be able to immediately envision, recognize or predict the structure of facilitator moieties that have the function of facilitating passage of polypeptides into cells. Similarly, one of skill in the art would also not be able to predict which modifications of signal peptides would result in peptides with this function, or which partial sequences of signal peptides would have this function. In this case, while the specification discloses peptide species, such as the penetratin peptide that has the function of facilitating passage of polypeptides into cells, these species would not be considered to be representative of the claimed genera because the claimed genera need not comprise any particularly identifying structural feature that correlates with the function of facilitating passage of polypeptides into cells

Although the skilled artisan could potentially screen for other “moieties", “modified signal peptides” or “partial sequences of signal peptides" as encompassed by the claims to identify those that facilitate passage of polypeptides into cells, it is duly noted that the written description provision of 35 U.S.C § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

In summary, given the lack of particularity with which the claimed “cancers”, "polypeptides" and “facilitator moieties” which are recited in the claimed methods, are described in the specification, it is submitted that the skilled artisan could not immediately envision, recognize or distinguish at least most of the members of the claimed genera to which the claims are directed; and therefore the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed methods at the time the application was filed.

11. Claims 1, 86-96 and 98-107 are rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for** methods of treating human cancers that express ERK2 in a mammal, comprising administering to said mammal an effective amount of a polypeptide consisting of the amino acid sequence of RSKAKWQTGTNPLYR (SEQ ID No: 4) or RSKAKNPLYR (SEQ ID No: 7), and **while being enabling for** methods of treating human cancers that express ERK2 in a mammal, comprising administering to said mammal an effective amount of a polypeptide consisting of the amino acid sequence of RSKAKWQTGTNPLYR (SEQ ID No: 4) or RSKAKNPLYR (SEQ ID No: 7), wherein the polypeptide is further coupled to a signal peptide with the amino acid sequence of AAVALLPAVLLALLA, **does not *reasonably* provide enablement for** the full scope of the claimed methods. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

MPEP § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to make and/or use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

The scope of the claimed methods is described supra.

As a first point, because the specification does not contain any specific, non-general guidance that would allow one if skill in the art to make the genera or subgenera of "polypeptides that binds to a binding domain of the MAP kinase for a cytoplasmic binding domain of β integrin subunit for the MAP kinase" or the recited genera or subgenera of "facilitator moieties that facilitate passage of the polypeptide across the outer cell membrane of the cancer cells" which would be representative of the full scope of these genera or subgenera, one of skill in the art would not be enabled to make the

full scope of such polypeptides or facilitator moieties without undue experimentation as evidenced by the teachings of Tame, Dixon, Lensink et al, Jones and Tosatto et al (supra); and if the full scope of polypeptides or facilitator moieties cannot be made without undue and/or unreasonable experimentation, the specification would not reasonably enable the skilled artisan to use the claimed polypeptides or facilitator moieties in the claimed methods without undue experimentation.

Secondly, it is noted that even while the elected invention is drawn to administering to a mammal an effective amount of a polypeptide consisting of the amino acid sequence of RSKAKWQTGTNPLYR or RSKAKNPLYR, and the specification teaches that these polypeptides are effective to inhibit the growth of human cancer cells expressing ERK2, the claims are broadly drawn to treating any cancer from any species expressing any MAP kinase (see e.g., claim 1). In this case, as evidenced by Tame, Dixon and Lensink et al (supra), it is highly unpredictable whether these polypeptides would bind to other MAP kinases which broadly include MAP kinases from any species and therefore, it is highly unpredictable whether these polypeptides could be used to treat the full scope of cancers expressing these diverse MAP kinases. Accordingly, one of skill in the art would be subject to undue and unreasonable expectation to determine how to treat the full scope of cancers encompassed by the claims with these polypeptides.

In this case, the specification does not provide any specific non-general guidance as to how to treat the full scope of cancers in mammals with the full scope of "polypeptides that binds to a binding domain of the MAP kinase for a cytoplasmic binding domain of β integrin subunit for the MAP kinase". For this reason, the specification would not reasonably enable the skilled artisan to use the full scope of the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Applicant is reminded that reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

In deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling

disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enable the skilled artisan to make and/or use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1, 86-94 and 98-107 are rejected under 35 U.S.C. 102(b) as being anticipated by Agrez (WO 2001/000677 A1, 2001, IDS filed 4/13/06).

The claims are herein drawn to methods comprising treating a mammal with colon cancer that expresses ERK2 with an effective amount of a polypeptide consisting of the amino acid sequence of RSKAKWQTGTNPLYR (SEQ ID No: 4) or RSKAKNPLYR (SEQ ID No: 7), wherein β6 integrin is essentially not expressed by the cancer cells. The claims are further herein drawn to the polypeptide coupled to a peptide moiety that facilitates the polypeptide's passage into the cancer cells and that this moiety comprises a partial sequence from a signal peptide or modified form thereof.

In this case, there is no limit on the modifications or the amount of sequence from signal peptide, so the claims broadly, but reasonably encompass any peptide moiety that facilitates the polypeptide's passage into the cancer cells because any such peptide could be modified from a signal peptide given that there are no limits on the number of modifications. Finally, the claims are herein drawn to the polypeptide being administered subcutaneously. As set forth above, the recitation of the integrin being essentially not expressed by the cancer cells is indefinite because it is unclear what level of expression of the integrin is considered as being essentially not expressed by the cancer cells. Accordingly, as the claims allow expression of the integrin and it is unclear how much expression is encompassed by the integrin being essentially not expressed by the cancer cells, the claims are broadly, but reasonably herein drawn to treating colon cancers were β6 integrin is expressed or not expressed by the cancer cells.

Agrez teaches methods comprising treating a mammal that has a human colon canncer expressing ERK2 with an effective amount of a polypeptide inhibitor of ERK2 consisting of the amino acid sequence of RSKAKWQTGTNPLYR or RSKAKNPLYR, wherein the polypeptide is further coupled to a penetratin peptide that facilitates the polypeptide's passage into the cancer cells and that the polypeptide is administered subcutaneously. (see entire document, e.g., pages 13, 23, 24, 54, 55 and 60). Notably, Agrez teach that 50% of colon (bowel) cancers express β6 integrin (see page 37), so Agrez teaches treating colon cancers with an effective amount of a polypeptide inhibitor of ERK2 consisting of the amino acid sequence of RSKAKWQTGTNPLYR or RSKAKNPLYR when β6 integrin is expressed or not expressed by the colon cancer cells. Therefore, the processes of Argrez are manipulatively and materially indistinguishable from the instantly claimed processes.

Accordingly, because the methods disclosed in the prior art are manipulatively and materially indistinguishable from the instantly claimed methods, absent a showing of any difference, the methods disclosed by the prior art anticipate the claimed methods.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

16. Claims 1 and 93-96 are rejected under 35 U.S.C. 103(a) as obvious over Agrez (WO 2001/000677 A1, 2001, IDS filed 4/13/06) in view of Nadler et al (US 5,877,282, 1999).

The scope of Claims 1 and 93-94 is set forth supra. Claims 95 and 96 are herein further drawn to the polypeptide coupled to a growth factor signal peptide moiety that comprises the amino acid sequence of AAVALLPAVLLALLA, which facilitates entry of the polypeptide into the cells.

Agrez teaches what is set forth in the above 102(b) rejection.

Notably, while Agrez teaches coupling the polypeptide to a penentrtin peptide to facilitate entry of the polypeptide into cells, Agrez does not expressly teach the growth factor signal peptide with the amino acid sequence of AAVALLPAVLLALLA as a peptide that can facilitate entry of the polypeptide into cells.

This deficiency is made up for in the teachings of Nadler et al. Nadler et al teach

that it is known in the art that the growth factor signal peptide with the amino acid sequence of AAVALLPAVLLALLA can be coupled to other polypeptides to facilitate entry of the polypeptide into cells (see entire document, e.g., column 8 and claim 7).

Thus, in view of these references, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made because coupling the growth factor signal peptide with the amino acid sequence of AAVALLPAVLLALLA to other polypeptides to facilitate entry of the polypeptide into cells was known and predictable in the art. Accordingly, one of ordinary skill in the art would not have found it inventive to predictably substitute the penetratin peptide for the growth factor signal peptide with the amino acid sequence of AAVALLPAVLLALLA, because they would have immediately envisioned that either peptide would be predictably effective in facilitating entry of the polypeptide into cells.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Double Patenting

17. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

18. Claims 1, 86-96 and 98-107 are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 217, 218, 219, 225, 238, 277 of copending Application No. 10/019,816 in view of Nadler et al (US 5,877,282, 1999). Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons:

The instant claims are described supra.

Claims 217, 218, 219, 225, 238, 277 of copending Application No. 10/019,816 are drawn to methods for inhibiting growth of colon cancer cells, the method comprising: treating a cancer cell with an effective amount of a polypeptide that binds the ERK2 MAP kinase consisting of the amino acid sequence of RSKAKWQTGTNPLYR or RSKAKNPLYR to inhibit the growth of the cancer cell and, wherein the polypeptide is coupled to a facilitator moiety that facilitates passage of the polypeptide across the outer cell membrane of the cancer cell into the cytoplasm of the cancer cell.

While the claims do not further define the location of the cancer cells, it is noted that the specification of '816 discloses that the colon cancer cells can be in a mammal (see page 24).

Notably, MPEP § 804.II.B.1 states that when considering obviousness-type double patenting issues, the disclosure of the patent [or copending application] cannot be used as prior art, but "[t]his does not mean one is precluded from all use of the patent disclosure". MPEP § 804.II.B.1 continues, "[t]he specification can always be used as a dictionary to learn the meaning of a term in the patent [or application] claim".

Citing *In re Vogel and Vogel*, 164 USPQ 619 (CCPA 1970), MPEP § 804.II.B.1 states, "one must first 'determine how much of the patent [or application] disclosure pertains to the invention claimed in the patent [or application]' because only '[t]his portion of the specification supports the patent claims and may be considered' " and " 'this use of the disclosure is not in contravention of the cases forbidding its use as prior art, nor is it applying the patent as a reference under 35 U.S.C. 103, **since only the disclosure of the invention claimed in the patent may be examined**" [emphasis added]. Consistently, in this instance, the examiner used only that portion of the copending application disclosure that pertains to the claimed invention.

Further addressing *In re Vogel and Vogel*, the Court decided the correctness of the conclusion that a patent claim drawn to a process for packaging "pork" would be obvious over a pending claim drawn to a process for packaging "meat", since although "pork does not read on "meat", "meat" reads literally on "pork". However, the Court further noted "viewing the inventions in reverse order, i.e., as though the broader claims issued first, does not reveal that the narrower (pork) process is in any way unobvious over the broader (meat) invention disclosed and claimed in the instant application" *Id*. at 623. The examiner believes this is because, were the patent claim to broadly recite "meat", although "pork" does not read on "meat" (i.e., a species encompassed by the genus generally does not suffice to describe the genus), the specification states how the claimed process is to be carried out with "pork". The Court indicated that this portion of the specification, stating how the claimed process is to be carried out using pork, supports the patent claims *and may be considered*. *Id*. at 622.

In certain situations, the supporting disclosure may be used to define terms in a claim and to determine whether the invention claimed has been modified in an obvious or unobvious manner. See *Carman Industries, Inc. v. Wahl et al.*, 220 USPQ 481 (CA FC 1983). If modified in an unobvious manner, there is no double patenting issue. In this instance, there can be no mistake that the invention claimed in the instant application is an obvious "variant" of the invention claimed in the patent, because the supporting disclosure of the latter teaches that colon cancer cells in a mammal would be encompassed by the claimed invention.

If the instant claims were drawn instead to an unobvious "variant", or to an invention that might only be gleaned from consideration of portions of the disclosure that do not support the copending claims, such that the consideration would be improper, then there would be no double patenting issue. Because only those portions of the disclosure that support the copending claims has been considered, and those portions include a description of the "variant" claimed in the instant application, then, double patenting rejection is believed warranted.

Finally, for the reasons set forth in the above 103(a) rejection, based on the teachings of Nadler et al, it is also submitted that the growth factor signal peptide with the amino acid sequence of AAVALLPAVLLALLA of claims 95 and 96 would be considered an obvious "variant" of claims 217, 218, 219, 225, 238, 277 of '816

Accordingly, the claimed inventions are so substantially similar that for the most part, the claimed subject matter of the patent anticipates the claimed subject matter of the instant application and any minor differences in the subject matter claimed in the instant application would be seen as an obvious variation of the subject matter claimed in the patent.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

19. No claims are allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brad Duffy whose telephone number is (571) 272-9935. The examiner can normally be reached on Monday through Friday 7:00 AM to 4:30 PM, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Respectfully,
Brad Duffy
571-272-9935

/Stephen L. Rawlings/
Primary Examiner, Art Unit 1643

/bd/
Examiner, Art Unit 1643
July 3, 2010